USE OF A TMDD MODEL TO SUPPORT DOSE SELECTION: GA101 EXAMPLE

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GA101: A glycoengineered CD20 antibody

- Rituximab: central therapy - type I antibody
- Preclinical studies: GA101 superior to Rituximab in inhibiting tumour cell growth in lymphoma xenograft model

**Increased direct cell death**
Type II versus Type I antibody

**Enhanced Antibody-Dependant Cell-mediated Cytotoxicity**
Glycoengineering for increased affinity to FcγRIIIa

**Lower Complement Dependant Cytotoxicity activity**
Type II versus Type I antibody

Phase I/II database at the time of dose and schedule selection

Two phase I/II monotherapy studies
One phase I combotherapy study

N=160 patients and 4018 concentrations

Population
- Indolent NHL
- Aggressive NHL
- Relapse patients
- CLL (n=34)

Doses
- 50-2000 mg
- N=3-20/cohort

Regimen
- q3w, 8 or 6 cycles
- qw, 4 cycles

CLL: Chronic Lymphocytic Leukemia, NHL: Non-Hodgkin Lymphoma
PK concentrations contain information on target.

- PK variability decreases with increased dose
- PK variability increases with tumour burden at baseline

GA101 concentrations apparently higher in responder patients

By dose level

By category of tumour size at baseline

By response status
Target-mediated disposition model: A quantification of the relationship between drug exposure and target binding

General model (Mager, JPP 2001)

- Only PK data are available
- An approximation of the model with assumption of quasi steady-state was used (Gibiansky, JPKPD 2008, Ma Pharm res 2012)
Target-mediated disposition model predictions

- Based on theoretical results, the PK model quantifies the decrease in free target related to drug exposure

**Dose-effect relationship**

**Faster target saturation with loading dose strategy**
Dose selection based on free target fraction

The free target fraction is lower in responders

<table>
<thead>
<tr>
<th>Responders</th>
<th>Median</th>
<th>P5-P95</th>
</tr>
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<tbody>
<tr>
<td>Free target fraction at steady-state</td>
<td>0.02</td>
<td>0.01-0.05</td>
</tr>
<tr>
<td>$C_{\text{trough}}$ (steady-state)</td>
<td>550 μg/mL</td>
<td>244-1298</td>
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- Aim: Fraction of free target below 0.05

- The targeted concentrations derived from the model are consistent with the xenograft model predictions (300-600 ug/mL)
Phase III trial: A dose of 1000 mg achieves high target saturation

- A dose of 1000 mg q3w with two loading doses on days 7 and 15 results in high target saturation i.e. below 0.05 from day 15 onwards
- 70% of the patients below 5% and 80% below 8%
- Allow outpatient administration
Continuing story: After TMDD..

- **Tumor size**: Greater reduction at high dose under monotherapy
- **End of treatment response**: High (1600/800 mg) vs. low dose (400/400 mg) responders
  - Heavily pre-treated indolent NHL: 55 % vs 17 %
  - Heavily pre-treated aggressive NHL: 32 % vs 24 %
Conclusion:

Use of TMDD model allowed to predict unobserved target suppression and support dose selection that is currently tested in Phase III.

**Strengths**
- Target-mediated disposition model used to elicit target information from concentrations.
- Particularly useful in early development when clinical efficacy data are limited.

**Limitation**
- No observed data yet for model validation.
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PD endpoint: Feasibility assessment

**Pharmacodynamics: B-cells**
Rapid, strong and sustained depletion
No clear dose/effect relationship